Remarks

Claims 38-49, 81-90, and 98-102 are pending in the application. Claims 43-48 are withdrawn from consideration. Claims 39-42, 49, 81-90, and 98-102 stand rejected. Claim 102 is objected to.

Claims 38, 84, 101, and 102 have been amended. Support for the Amendment to claim 38 can be found throughout the specification, for example, in Examples 4-8. Claim 84 has been amended to clarify the language of that claim. Claims 101 and 102 have been amended to correct the dependencies of those claims.

No new matter has been added by the present Amendment. Applicant specifically reserves the right to pursue the subject matter of the canceled or amended claims in a related application. The present Amendment is introduced for the sole purpose of furthering prosecution. Applicant respectfully requests reexamination and reconsideration of the case in light of the present Amendments and the following remarks. Each of the rejections levied in the Office Action is addressed individually below.

Objection to the Claims

The Examiner has objected to claim 102 on the grounds that it is improper because a multiply-dependent claim cannot depend from another multiply-dependent claim. Applicant apologizes for this inadvertent error and submits that Applicant intended for claim 102 to depend from claim 100, not 101. Applicant has amended claim 102 so that it depends from claim 100 (which is not a multiply-dependent claim). Applicant, therefore, respectfully submits that the objection is rendered moot by the present Amendment.

Rejection under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite

Claim 101 stands rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Examiner points out that claim 101 is dependent from claim 101. Applicant apologizes for this inadvertent error and submits that Applicant intended claim 101 to depend from claim 100, as the Examiner suggested in the Office Action. Applicant has amended claim 101 so that it depends from claim 100. Applicant, therefore, respectfully submits that the objection is rendered moot by the present Amendment.

Rejections under 35 U.S.C. § 103(a) as allegedly being obvious

Claims 38-42, 49, 81-90, and 98-101 stand rejected under 35 U.S.C. § 103(a) on the ground that they are unpatentable over Abe *et al.* (2001, *Eur. J. Pharm. Sci.*, 13:61-69) and three additional references, *i.e.*, Tuschl *et al.* (PCT Patent Publication WO 02/44321), Astriab-Fisher *et al.* (2000, *Biochem. Pharmacol.*, 60:83-90), and Deonarain *et al.* (1998, *Expert Opin. Ther. Patents*, 8:53-69).

Claims 38-42, 81-83, 98, 100, and 101 stand rejected under 35 U.S.C. § 103(a) on the ground that they are unpatentable over Agrawal *et al.* (U.S. Patent Number 5,194,428) and the same three additional references, *i.e.*, Tuschl, Astriab-Fisher, and Deonarain.

The Examiner cites Abe in the first rejection as teaching antisense molecules that target the influenza nucleoprotein (NP) gene, and cites Agrawal in the second rejection as teaching antisense molecules that target the influenza PB1 gene. In levying both rejections, the Examiner acknowledges that neither Abe nor Agrawal teaches (1) using siRNA targeted to viral nucleoprotein or PB1, (2) using an siRNA and a cationic peptide, (3) administration by inhalation or as an aerosol, and (4) using an antibody or ligand to specifically target a cell. In both rejections, the Examiner utilizes the remaining three references, *i.e.*, Tuschl, Astriab-Fisher, and Deonarain to remedy these defects. The Examiner states that it would have been obvious to combine Abe or Agrawal with Tuschl, Astriab-Fisher, and Deonarain to arrive at the claimed invention. Applicant respectfully disagrees.

The Examiner cites Tuschl as teaching (1) that siRNAs are the new alternative to antisense compounds, (2) a method of using siRNA to infect cells of mammals and modulation of function of a viral target gene, (3) that siRNAs have improved efficacy and safety, (4) that siRNAs can be delivered using a carrier system and administered by injection or intranasally, and (5) vectors capable of expression of an siRNA. The Examiner states that it was well known at the time when the present application was filed that silencing of gene expression using siRNA was more efficient and sequence-specific as compared to antisense technology. The Examiner states that it would have been obvious to substitute an siRNA molecule for the antisense molecule in the method taught by Abe.

The Examiner cites Astriab-Fisher as teaching inhibition of gene expression using oligonucleotides conjugated to cationic peptides. The Examiner states that it would have been obvious to deliver siRNA (as taught by Tuschl) that targets influenza virus NP or PB1 (as taught by Abe or Agrawal) using cationic peptides taught by Astriab-Fisher.

Finally, the Examiner cites Deonarain as teaching advantages of using ligand-targeted receptor polyplexes for delivery of nucleic acids to specific cells and tissues. The Examiner states that it would have been obvious to deliver siRNA (as taught by Tuschl) that targets influenza virus NP or PB1 (as taught by Abe or Agrawal) using cationic peptides (as taught by Astriab-Fisher) and an antibody that specifically targets lung cells, as taught by Deonarain.

Applicant respectfully disagrees with the Examiner's position and respectfully submits that no combination of these references can render the present claims obvious. Indeed, Applicant respectfully submits that, contrary to the Examiner's assertion on pages 6-7 of the Office Action, there would be no reasonable expectation of success at using a cationic peptide for delivery of siRNA to cells.

As an initial matter, Applicant respectfully submits that it would not have been obvious to one of ordinary skill in the art to substitute an siRNA (as taught by Tuschl) for an antisense oligonucleotide (as taught by Abe or Agrawal). Indeed, siRNAs and antisense oligonucleotides have different structural characteristics. For example, siRNAs are substantially double-stranded, and antisense oligonucleotides are single-stranded. Applicant respectfully submits that it would *not* be obvious to simply switch one molecule type for the other.

Indeed, even if it *were* obvious to try to switch siRNAs for antisense oligonucleotides for the purpose of *inhibiting gene expression*, it would *not* be obvious to try to switch siRNA for antisense oligonucleotides with respect to a *mode of delivery*. One of ordinary skill in the art would have no reason to believe that the effectiveness of a given delivery method for delivery of an agent having certain structural characteristics would predict or correlate with the effectiveness of the same delivery method for delivery of an agent having *different structural characteristics*. Thus, one of skill in the art would have no reason to believe that delivery methods that are successful for *single-stranded* oligonucleotides would also be successful for substantially *double-stranded* siRNAs.

Indeed, Applicant notes that that the reference that the Examiner cites as teaching inhibition of gene expression using oligonucleotides conjugated to cationic peptides (*i.e.*,

Astriab-Fisher) describes experiments using *single-stranded*, antisense oligonucleotides. In contrast, the siRNAs recited in the present claims are structurally different; they are substantially *double-stranded*. As established above, one of skill in the art would have no reason to believe that delivery methods that are successful for *single-stranded* oligonucleotides would also be successful for substantially *double-stranded* siRNAs. Thus, one of skill in the art would have no reason to believe that the methods described in Astriab-Fisher for delivery of antisense oligonucleotides would be useful for delivery of siRNA.

Applicant further notes Astriab-Fisher describes only *in vitro* methods. Astriab-Fisher describes use of cationic peptides to deliver antisense oligonucleotides *directly to cells in culture*. Astriab-Fisher describes a simple experimental system, consisting essentially of cells, antisense oligonucleotides, cationic peptides, and cell culture media. Experiments performed under such conditions are hardly predictive of whether cationic peptides would successfully deliver a *structurally different* entity (*e.g.*, an siRNA) to cells when administered to an *entire organism*. Living organisms are much more complicated than simple cell culture systems, and as such, introduce many more variables that can interfere with successful delivery. One of skill in the art would certainly not predict that a method for delivering a *single-stranded oligonucleotide* to cells *in culture* would be successful for delivery of a *double-stranded siRNA* to cells within the context of an *entire organism*. By contrast, the present specification presents data which, in fact, demonstrate that cationic peptides are successful for delivery of *siRNA* to cells when administered to a *mouse in vivo* (see Example 4, paragraphs 239-253, which exemplifies poly-L-lysine).

Finally, Applicant points out that Deonarain does not remedy any of the defects described above relating to the combination of Abe or Agrawal with Tuschl and Astriab-Fisher. Applicant submits that none of these five references, alone or in combination with one another, renders the present claims obvious. Applicant respectfully requests that the rejection be removed.

Rejection under 35 U.S.C. § 112 for lack of written description

Claims 38-42 stand rejected by the Examiner under 35 U.S.C. § 112, first paragraph, for alleged lack of written description. The Examiner states that the specification does not adequately support claims drawn to methods of inhibiting any transcript associated with any influenza virus. Applicants respectfully disagrees.

Claims 49, 84-90, and 99 were rejected on the same grounds in the Office Action mailed March 11, 2008. In that Office Action, the Examiner had suggested claim amendments that would serve to overcome the rejection. Applicant made the suggested claim amendments, and the Examiner subsequently withdrew the written description rejection of claims 49, 84-90, and 99. Thus, *solely* in order to further prosecution and without agreeing with the Examiner's position, Applicant is willing to make the Examiner's suggested claim amendments to overcome the written description rejection of claims 38-42. Applicant, therefore, has amended independent claim 38 to specify that the influenza target transcript is an influenza nucleoprotein (NP) transcript. Applicant, therefore, respectfully requests that the rejection be removed.

Obviousness-Type Double Patenting

The Examiner has levied a *provisional* obviousness-type double patenting rejection, asserting that claims 38-42, 49, 81-90, and 90-100 pending in the present application are not patentably distinct from claims 12, 22, and 24-27 of co-pending U.S. application U.S.S.N. 11/259,434.

Applicant respectfully refrains from commenting on this rejection until such time as it matures into an *actual* rejection. Given the amendments to the present claims, and the potentially changing nature of the claims in the cited applications, comment at this time would not be prudent.

Conclusion

For all of the reasons set forth above, each of the rejections in this case should be removed and the application should proceed to allowance. A Notice to that effect is requested.

If, at any time, it appears that a phone discussion would be helpful, the undersigned would greatly appreciate the opportunity to discuss such issues at the Examiner's convenience.

Please charge any fees that are *necessary* to maintain pendency and/or protect the filing date of the present application to our Deposit Account Number 03-1721, referencing Attorney's Docket Number 0492611-0507 (MIT 10396). To the extent that there are any discrepancies between what Applicant has paid with the filing of the present Application and what the USPTO believes is owed, Applicant respectfully requests that a Notice be issued explaining any such discrepancy.

Respectfully submitted,

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